Frederick National Laboratory for Cancer Research, Frederick, MD

Biopharmaceutical Development Program

Standard Operating Procedure

Title: Format and Contents of a Technology Transfer Package

SOP Number: 25103

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Originator/Date: [redacted]

Approval/Date: [redacted]

Approval/Date: [redacted]

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1.0 Purpose

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1.0 Purpose

This procedure establishes minimum requirements for the format and content of the package of information submitted to Good Manufacturing Practices (GMP) Manufacturing or Production groups of the Biopharmaceutical Development Program (BDP) from development laboratories as a basis for the proposed manufacturing/purification process.

2.0 Scope

This procedure defines the format and basic requirements for the information package supplied to GMP Production/Manufacturing by the Development Laboratories in advance of any GMP campaign. This SOP governs the information transfer to GMP Fermentation, Recovery, and Manufacturing Groups in the BDP. The term “Manufacturing” used in this document is understood to mean Fermentation/Recovery, Virus Production, and GMP Purification unless otherwise indicated.

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Not all the information described herein may be appropriate or necessary for every project. The decision to exclude or amend the proposed content requirements will be evaluated on a case-by-case basis. Deviations from the SOP requirements must be justified and approved in advance of the submission and review of the final document.

It is the responsibility of the Project Scientist to ensure that the proposed process and raw materials or components used in the proposed process comply with regulatory requirements and applicable Food and Drug Administration (FDA) Guidelines and Guidances. Animal-derived materials must be avoided unless absolutely necessary. Product-contact raw materials and components must be traceable.

3.0 Authority and Responsibility

3.1 The Director, **Program and Technical Director of BDP** has the authority to establish this procedure.

3.2 The **Program and Technical Director of BDP** is responsible for the implementation of this procedure, ensuring that training is performed on this procedure, and providing training documentation to Biopharmaceutical Quality Assurance (BQA).

3.3 It is the responsibility of the author(s) of any technical transfer document to ensure all raw materials and components are Current Good Manufacturing Practice (CGMP) compliant. Animal-derived materials must be avoided unless absolutely necessary. Non-traceable, animal derived products are prohibited.

3.4 BQA is responsible for quality oversight of this procedure.

4.0 Format

4.1 Use only 12-point Arial font for typing Technology Transfer Packages.

4.2 All pictures of gels must be color copies or black and white photos, not black and white Photostats. The figure must be a true and accurate representation of the original. Densitometry scans can be used as supplementary information but not as a substitute.

4.3 Charts must be free-standing and clearly labeled.

5.0 Organization

5.1 Cover Page(s) (See **Attachment 1**).

5.1.1 Project/Product name and number.

a) Principal Investigator (e.g., Dr. [redacted]).

b) NCI/BRB Project Director (e.g., Dr. Anthony Welch).

c) Author(s) Signature – individuals involved in the development of the process, new testing assays, and/or the preparation of the document. Their signature attests to the technical accuracy of the contents.

d) Reviewer Signature – the Project Scientist or designee who has reviewed the contents for technical accuracy.

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e) Manufacturing Signature – The GMP Manufacturing Groups' acceptance of the document. This signature implies that the proposed process has been reviewed and deemed appropriate for Manufacturing's resources and constraints.

f) BQA – If product is intended for pre-clinical studies, GLP, or human clinical trials, GMP.

g) Date – the date the document was turned over to Manufacturing.

h) Date(s) of all revisions, modifications or additions of subsequent data or pertinent process related information. The rationale for the modification must be submitted along with the additional information.

5.2 Executive Summary

a) Identify the Product.

b) Provide a Brief Project History: When accepted officially as a project, turned over to Development, etc.

c) State what is known about it (e.g., pI, Molecular Weight, Extinction Coefficient).

d) Indicate the intended use: (e.g., R&D, animal studies, non-human primate studies, IND-Directed Toxicology, Human Clinical Trials, or describe use).

e) List the deliverables: total amount, concentration, formulation, etc.

f) Viral burden information, if known.

g) Bioburden list: what it is, how much, risk to product or operator.

h) Safety issues – biohazards and other hazards associated with the Product or reagents/buffers used in its manufacture. Indicate if Material Safety Data Sheets (MSDS) are available.

i) Supporting Documentation – Publications, abstracts, grant or NExT proposals, patents, etc., that serve to enhance an understanding of the product and its intended use.

5.3 Table of Contents (see **Attachment 2**).

5.4 Table of Figures. All tables, figures, printouts of hard data, and chromatograms referenced in the text are listed here as well as their location in the document. All figures should be free standing and clearly refer to the location in the text where they are discussed (see **Attachment 3**). Section 4b. Table of Tables, photographs, etc.

5.5 Contaminant Removal Table (see **Attachment 5**).

5.6 Process Flow Chart – as per ***SOP 21415 - Preparation and Approval of Master Production Records***. This should be directly transferable into the Batch Production Record (BPR). It shows each of the individual process steps as well as any in-process or Process Analytic (PA) testing that will be required at that step. Clearly indicate critical tests and specifications, if any.

5.6.1 Describe the purpose of each step in the right-hand margin(s), (e.g., low pH – viral inactivation; flow thru Q – removal of DNA and endotoxin).

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5.6.2 Describe the required in-process or PA testing in the right-hand margin.

5.6.3 Critical Parameters – for each process step, repeat what critical issues can affect the yield, purity or safety of the product.

5.7 Process Description – Comparable to the Process Overview of a CMC Section (see **Attachment 3**). This section describes in narrative form the overall process.

5.8 Detailed Process Description. A description in detail about each individual process step. Where necessary, parameters which are critical to achieving a successful outcome should be identified as a specification to be included in the Manufacturing BPR. Other parameters should be identified as recommendations and a justification provided for the suggested set point and operating ranges. The Development Notebook citation which covers the development of the process step should also be included as reference material, if appropriate (e.g., notebook number, page or dates, etc.). For each phase of the process, address the following:

a) What does this step do? Identify critical parameters and required testing.

b) Reference what was investigated but not selected.

c) What was used – resin, equipment, media, buffers, cells (passage number and type).

d) Process control description: set point and ranges, including, but not limited to, temperature, pH and conductivity, sparging volume per volume per minute (vvm), agitation rates, pressures. For nucleic acid or virus-based products, describe culture conditions, seeding densities, and maximum passage numbers.

e) Column height, width-to-height rations, linear velocities, volumetric flow rates, loading capacity, etc.

f) Equilibration, load, wash and elution volumes as a function of packed resin volumes and OD absorbance units (if appropriate).

g) Chromatograms, Gels – labeled in detail as to times, and other pertinent information.

h) Overall duration for the process step.

i) Harvest/Stop/Collection methods and conditions.

j) Step yield and % purity; endotoxin content/mg.

k) Disposition of the product and recommendations for storage upon completion of the process Step (reference 5.15).

l) Schematics, if necessary, showing equipment layout and design specs.

5.9 Yield Table (see **Attachment 4**). Shows step-to-step and overall purity, volumes, etc.

5.10 Contaminant Removal Table. This table shows where in the process contaminants such as endotoxin, Deoxyribonucleotide Acid (DNA), Host Cell Proteins (HCP), etc. meet the proposed release specification or fall below the Limit of Detection (LOD) (see **Attachment 5**).

5.11 Proposed Scale-Up Plan (see **Attachment 6**). Scale-up plans for an intermediate batch size (pilot lot) and the final manufacturing batch size should be detailed in this section.

a) Proposed batch size.

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b) Buffers: part number, chemical name, common name, recommended specs. Required minimal estimated volumes and proposed ordering amounts.

c) Raw material COAs. Identify animal-derived materials and the source of material described (e.g., organs, tissues).

d) Resins.

e) Column sizes, packing pressures and flow rates.

f) Height-to-width ratios.

g) Amount of bulk material needed to make the final batch deliverable.

h) Recommended sampling plan; volumes and storage conditions for virus removal samples, PA samples and in-process testing samples.

i) Minimum volumes for washing and post-load rinsing.

j) Loading rates expressed as both linear velocity and volumetric rates.

k) Times/durations expected for each step based on factors such as the linear velocity, estimated load volumes, etc.

l) ODs for seed transfer ferment or feeding schedule and termination criteria.

5.12 New SOPs required – if any. Describe what the SOP is for and explain why it is needed.

5.13 Approved Master Specification. For bulk and vialed product or intermediates for further manufacturing use. Bold assays currently under development. Describe any new assays along with a plan for transfer and validation or qualification to PA.

5.14 Results of any in-process or final product testing that demonstrate that the specifications are achievable.

5.15 In-Process Stability testing: (e.g., pH stability for viral inactivation). Product stability during each of the proposed holding points should be investigated and appropriate assays used to justify the claim. If possible, the material should be tested to failure. Include all supporting data, such as gels, chromatograms, potency assays, etc. Minimum/maximum hold times must be described.

5.16 Formulation and Stability Studies on final purified product, describe stability-indicating assays, if known.

5.17 Product-handling procedures. Describe in detail proper conditions for storage, thawing, and reconstitution and other uses.

5.18 Troubleshooting – A table that describes what has been observed that has not been covered above; what it means, recommendations for remediation.

5.19 Supporting Documentation – Any ancillary information that is not directly supportive of the process but of value in explaining how choices were made (e.g., on resin versus another, buffer pH, etc.)

5.20 Distribution List – who has received a copy of the document and the date. The recipient's signature next to their printed name.

5.21 Material Safety Data Sheets.

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5.22 Virus Removal/Inactivation Plan.

5.22.1 Scaled-down study describing amount, location, and storage conditions for in-process sampling. PA and BQA signatures required.

5.23 Addenda and Revisions. Additional information and modifications to the original document must be submitted to all recipients of the original document.

5.24 Distribution and Archiving: Completed and signed digital copy of the Technology Transfer document should be saved in the Project folder under Reports. A fully executed document should be printed and filed in the Project Files in the Documentation Room.

6.0 References and Related Documents

6.1 **SOP 21415** *Preparation and Approval of Master Production Records*

7.0 Attachments

7.1 **Attachment 1** Example Cover Page for a Technical Transfer Package

7.2 **Attachment 2** Example Table of Contents

7.3 **Attachment 3** Example Process Flow Chart

7.4 **Attachment 4** Example Yield Summary Table

7.5 **Attachment 5** Example Contaminant Removal Table

7.6 **Attachment 6** Example Proposed Manufacturing Scale

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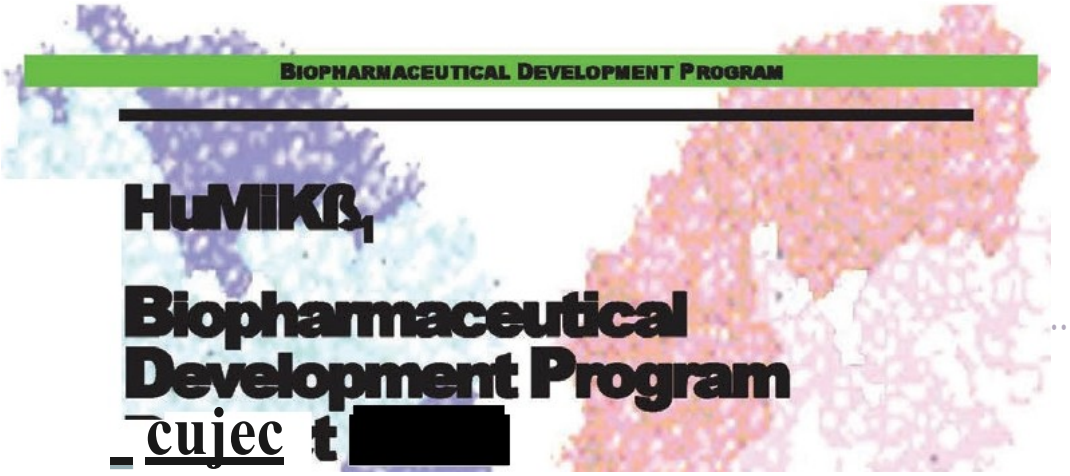
Attachment 1
Example Cover Page for a Technical Transfer Package



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Example Table of Contents

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I. Introduction

A. DESCRIPTION

The Humanized Mikß$_1$ (HuMikß$_1$) produced through the processes explained in detail within this package inhibits IL-15 binding and in conjunction with humanized anti-Tac is hoped be a new treatment for autoimmune diseases, graft-versus-host disease, and prevention of allograft rejection.[1] HuMikß$_1$ is an IgG1 produced in the human mouse hybrid cell line SP2/0-Ag14 (ATCC CRL 1581). The cells are grown in "CD Hybridoma Media without L-glutamine" with 4mM GlutaMax I added.

B. DELIVERABLE

The deliverable product to the principal investigator is 40grams of cGMP purified HuMikß$_1$ at 5mgs/ml in Phosphate Buffered Saline (PBS), pH 7.2, 10mls/vial, that will be used in human clinical trials.

C. SAFETY ISSUES

No known toxicity is associated with the product or the final formulation buffer.

D. CHARACTERISTICS

Biological, physiochemical, and biochemical characteristics known about HuMikß$_1$ include:

1. Currently, in culture, only type A virus particles present
2. The pI of the protein is 7.9 as determined by cIEF
3. The Molecular Weight is ~150,000 Da
4. The pH of the final vialed product is pH 7.2
5. The Extinction Coefficient is 1.4.

E. DEVELOPMENT HISTORY

A standard of HuMikß$_1$ was used to develop an HPSEC method of quantitation and purity. The standard (labeled as 8.5mgs/mL) given to the Purification Development Group from the Cell Culture Group was injected at known concentrations onto a G3000SWxl analytical column (Tosoh Biosep Catalog # 08541) with 0.1M $NaSO_4$, 0.1M $NaPO_4$, 0.3M NaCl, pH 7.0 as the mobile phase to generate a standard curve using the ÄKTA Chromatography System Unicorn Software[2] (Amersham Biosciences, Piscataway, N.J.). This standard curve can now be applied to all HPSEC injections of HuMikß$_1$, thus allowing the software to determine the concentration and purity of HuMikß$_1$ in any sample.

[1] See Attachment 1 - Humanized Mikß$_1$ Paper, J. Hakimi (et al.), The Journal of Immunology, vol 151, 1075-1085, No. 2, July 15, 1993
[2] See Attachment 2 - HPSEC Standard Curve for HuMikß$_1$ Generated on the ÄKTA

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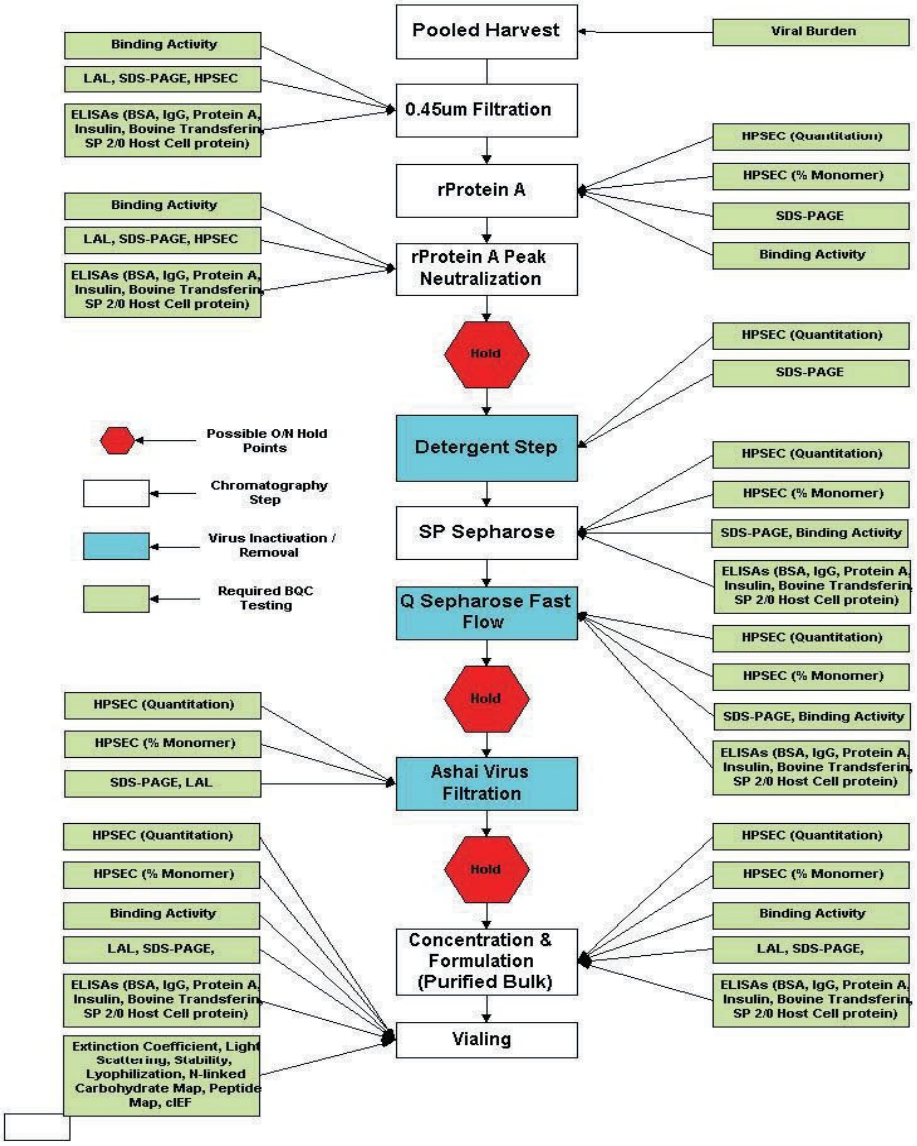
Attachment 3
Example Process Flow Chart

II. PROCESS FLOW CHART

Chart 1 – Process Flow Chart of 1/5 Scale HuMikβ$_1$ Proposed Manufacturing Batch



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Attachment 4
Example Yield Summary Table

IV. YIELDSUMMARY T ABLE

Table 1: HuMikfl.t Pilot Scale (lot #1 - Process Yield Summary

PROCESS STEP	STEP OUTPUT (mg)	STEP RECOVERY (%)	OVERALL RECOVERY (%)
Harvest (pooled)	14182mg	N/A	*NIA*
Harvest (filtered pool)	13865mg	97.8%	97.8%
Protein A Peak	10819mg	78.3%	76.3%
Neutralized & Diluted rProtein A Peak	10555mg	97.6%	74.4%
SP Sepharose Peak (after viral inactivation& filtration of load)	9345mg	88.4%	65.9%
Q Sepharose Flowthrough Peak	5035mg	98.9%	70.0%
Asahi Filtration	4954mg	99.1%	68.9%
TFF / Diafiltration / 0.45um Filtration	4208mg	85.1%	58.5%

NOTE: Output of the Q Sepharo5e Flow-through column (and therefore, the remaining two step5)affected by a technical error resulting in a 49% loss of the Q Sepharose load. The overall % re= verylisted for the last three steps is the expected % recovery assuming no error.

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Attachment 5
Example Contaminant Removal Table

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V. CONTAMINANT REMOVAL TABLE

Sample	BSA	Bovine IgG	Protein A	Insulin	Bovine Transferin	SP 2/0 Host Cell
Pooled Harvest	6.608	BLD	BLD	BLD	BLD	>200
Filtered Pooled Harvest	3.222	BLD	BLD	0.102	BLD	>200
Protein A Flow-through	4.491	BLD	48.78	1.024	BLD	>200
Protein A Peak	1.925	0.209	13.59	0.302	0.308	>200
Neutralized rProtein A Peak	6.862	BLD	12.14	0.002	BLD	>200
Diluted Neutralized rProtein A Peak	NT	NT	NT	NT	NT	NT
SP Sepharose Load (Run #1)	6.206	0.788	11.80	1.036	3.06	>200
SP Sepharose Flow-thru (Run #1)	6.248	0.976	10.52	2.299	4.361	42.50
SP Sepharose Peak (Run #1)	0.576	BLD	6.958	0.009	BLD	235.2
SP Sepharose Load (Run #2)	4.894	0.611	12.38	0.836	3.327	>200
SP Sepharose Flow-thru (Run #2)	7.158	0.953	7.643	1.592	4.38	38.03
SP Sepharose Peak (Run #2)	0.343	0.055	1.927	BLD	BLD	369.9
Q Sepharose Load	NT	NT	NT	NT	NT	NT
Q Sepharose Peak	BLD	BLD	BLD	0.342	BLD	177.2
Asahi Filtered Pool	1.444	0.150	0.072	BLD	BLD	369.4
TFF Pool	1.952	0.789	0.257	0.195	BLD	192.6
Purified Bulk (same as TFF Pool)	1.952	0.789	0.257	0.195	BLD	192.6

NOTES:

1) Unit for each test = ng/ml
2) NT = Not Tested
3) BLD = Below Level of Detection

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Attachment 6
Example Proposed Manufacturing Scale

VII. PROPOSED MANUFACTURING SCALE

1) Buffers

a) PBS, pH 7.0 — acceptable pH range: 7.0±0.1
b) 0.1M NaAc, pH 3.5 — acceptable pH range: 3.5±0.1
c) 20mM NaAc, pH 5.0 — acceptable pH range: 5.0±0.1
d) 20mM NaAc, 1M NaCl, pH 5.0 — acceptable pH range: 5.0±0.1
e) PBS, pH 7.2 — acceptable pH range: 7.2±0.1

2) Harvest

a) Start with ~80gm (80-90L) Harvest supernatant material frozen at –20°C
b) Thaw harvest material 24-36 hours at 2-8°C; if harvests not completely thawed, finish thawing in a 30°C water bath.
c) Filter for harvest

3) Protein A column

a) Protein A binding capacity: ~10mgs HuMikβ_1/mL resin
b) Flow rate = 30cm/hr
c) Equilibrate column with 2-3 CV PBS, pH 7.0
d) Wash rProtein A column with no less than 10 CV PBS, pH 7.0 after reaching baseline to remove virus particles and since the SP 2/0 Host Cell Protein ELISA results were higher than expected in Pilot Scale Run
e) Elute HuMikß$_1$ with 3-4 CV 0.1M NaAc, pH 3.5

4) Neutralization

a) Ratio of 1N NaOH to rProtein A peak is approximately 1:17
b) Acceptable pH range for neutralization: pH 5.0±0.1

5) Viral Inactivation

a) Concentration prior to Solvent-Detergent addition needs to be ≤2.0mgs/mL; if necessary dilute with 20mM NaAc, pH 5.0
b) Slowly swirl upon addition of 25X Solvent-Detergent then let sit at room temperature
c) Inactivation is for no less than 4 hours and no more than 24 hours

6) SP Sepharose column

a) Binding capacity: 4-5mgs/mL resin
b) Flow rate determined from results of column packing test (asymmetry and H_R values)
c) Charge column with 2-3 CV 20mM NaAc, 1M NaCl, pH 5.0
d) Equilibrate column with 2-3 CV 20mM NaAc, pH 5.0
e) Wash column with 2-3 CV 20mM NaAc, pH 5.0 after load
f) Elute HuMikß$_1$ with 2-3 CV 15% 20mM NaAc, 1M NaCl, pH 5.0

7) Q Sepharose column

a) Flow rate = 30cm/hr
b) Charge column with 2-3 CV 20mM NaAc, 1M NaCl, pH 5.0
c) Equilibrate column with 2-3 CV 20mM NaAc, pH 5.0
d) Wash column with 2-3 CV 20mM NaAc, pH 5.0 after load

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